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(54) Title: 2' AND 3'-NUCLEOSIDE PRODRUGS FOR TREATING FLAVIVIRIDAE INFECTIONS

(57) Abstract: 2' and 3'-Prodrugs of 1', 2', 3' or 4'-branched ß-D or ß-L nucleosides, or their pharmaceutically acceptable salts and derivatives are described, which are useful in the prevention and treatment of *Flaviviridae* infections and other related conditions. These modified nucleosides provide superior results against flaviviruses and pestiviruses, including hepatitis C virus and viruses generally that replicate through an RNA dependent RNA reverse transcriptase. Compounds, compositions, methods and uses are provided for the treatment of *Flaviviridae* infection, including HCV infection, that include the administration of an effective amount of the prodrugs of the present invention, or their pharmaceutically acceptable salts or derivatives. These drugs may optionally be administered in combination or alteration with further anti-viral agents to prevent or treat *Flaviviridae* infections and other related conditions.

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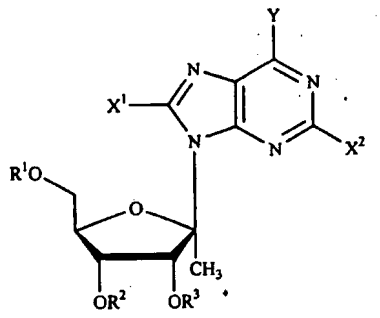
We claim.

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, of the formula:



(I)

wherein:

R^1, R^2 and R^3 are independently H, phosphate or a stabilized phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; an amino acid residue; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;

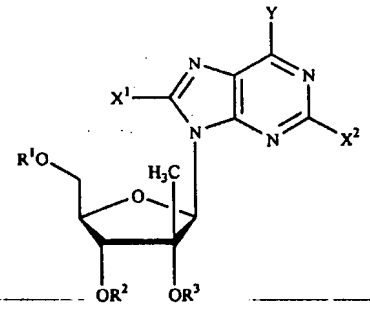
wherein at least one of R^2 and R^3 is not hydrogen;

Y is hydrogen, bromo, chloro, fluoro, iodo, OH, OR^4, NH, NHR^5, NR^4R^5, SH and SR^4;

X^1 and X^2 are independently selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OH, OR^4, NH, NHR^5, NR^4R^5, SH and SR^4; and

R^4 and R^5 are independently hydrogen, acyl, or alkyl.

2. A compound of Formula II, or a pharmaceutically acceptable salt of the formula:



(II)

wherein:

R^1, R^2 and R^3 are independently H, phosphate or a stabilized phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; an amino acid residue; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;

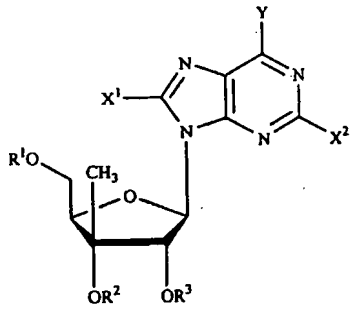
wherein at least one of R^2 and R^3 is not hydrogen;

Y is hydrogen, bromo, chloro, fluoro, iodo, OR^4, NR^4R^5 or SR^4;

X^1 and X^2 are independently selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR^4, NR^4NR^5 or SR^5; and

R^4 and R^5 are independently hydrogen, acyl, or alkyl.

3. A compound of Formula III, or a pharmaceutically acceptable salt thereof:



(III)

wherein:

R^1, R^2 and R^3 are independently H, phosphate or a stabilized phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; an amino acid residue; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;

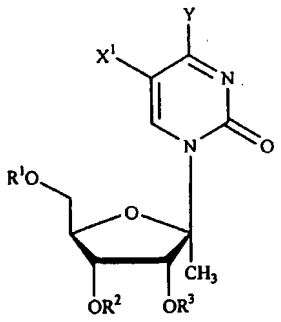
wherein at least one of R^2 and R^3 is not hydrogen;

Y is hydrogen, bromo, chloro, fluoro, iodo, OR^4, NR^4R^5 or SR^4;

X^1 and X^2 are independently selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR^4, NR^4NR^5 or SR^5; and

R^4 and R^5 are independently hydrogen, acyl, or alkyl.

4. A compound of Formula IV, or a pharmaceutically acceptable salt or prodrug thereof:



(IV)

wherein:

R^1, R^2 and R^3 are independently H, phosphate or a stabilized phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; an amino acid residue; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;

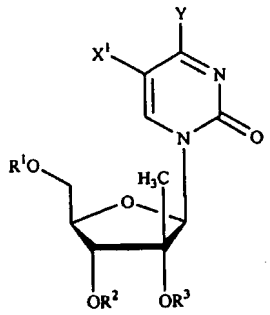
wherein at least one of R^2 and R^3 is not hydrogen;

Y is hydrogen, bromo, chloro, fluoro, iodo, OR^4, NR^4R^5 or SR^4;

X^1 is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR^4, NR^4NR^5 or SR^5; and

R^4 and R^5 are independently hydrogen, acyl, or alkyl.

5. A compound of Formula V, or a pharmaceutically acceptable salt or prodrug thereof:



(V)

wherein:

R^1, R^2 and R^3 are independently H, phosphate or a stabilized phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; an amino acid residue; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;

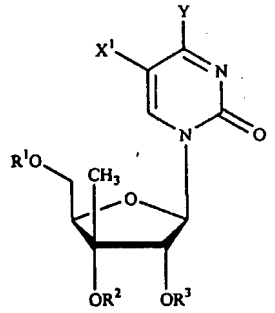
wherein at least one of R^2 and R^3 is not hydrogen;

Y is hydrogen, bromo, chloro, fluoro, iodo, OR^4, NR^4R^5 or SR^4;

X^1 is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR^4, NR^4NR^5 or SR^5; and

R^4 and R^5 are independently hydrogen, acyl, or alkyl.

6. A compound of Formula VI or a pharmaceutically acceptable salt or prodrug thereof:



(VI)

wherein:

R^1, R^2 and R^3 are independently H, phosphate or a stabilized phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; an amino acid residue; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;

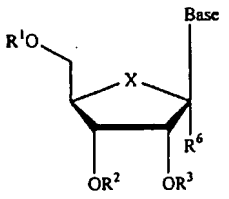
wherein at least one of R^2 and R^3 is not hydrogen;

Y is hydrogen, bromo, chloro, fluoro, iodo, OR^4, NR^4R^5 or SR^4;

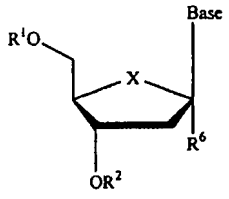
X^1 is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, chloro, bromo, fluoro, iodo, OR^4, NR^4NR^5 or SR^5; and

R^4 and R^5 are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl and cyclopropyl).

7. A compound selected from Formulas VII and VIII, or a pharmaceutically acceptable salt or prodrug thereof:



(VII)



(VIII)

wherein:

Base is a purine or pyrimidine base;

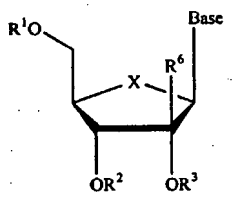
R^1, R^2 and R^3 are independently H, phosphate or a stabilized phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; an amino acid residue; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;

wherein R^2 is not hydrogen;

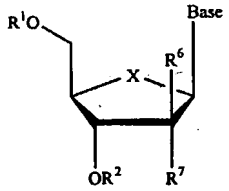
R^6 is alkyl, CH_3, CF_3, azido, cyano, alkenyl, alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, chloro, bromo, fluoro, iodo, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

X is O, S, SO_2 or CH_2.

8. A compound of Formulas IX and X, or a pharmaceutically acceptable salt:



(IX)



(X)

wherein:

Base is a purine or pyrimidine base;

R^1, R^2 and R^3 are independently H, phosphate or a stabilized phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; an amino acid residue; a carbohydrate; a peptide; cholesterol; or a pharmaceutically

acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;

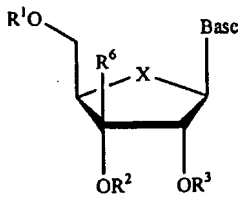
wherein R^2 is not hydrogen;

R^6 is alkyl, CH_3, CF_3, azido, cyano, alkenyl, alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, chloro, bromo, fluoro, iodo, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

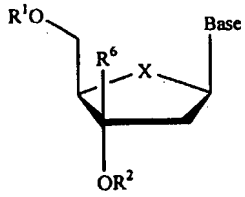
R^7 is hydrogen, OR^3, hydroxy, alkyl, azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

X is O, S, SO_2 or CH_2.

9. A compound selected from Formulas XI and XII, or a pharmaceutically acceptable salt thereof:



(XI)



(XII)

wherein:

Base is a purine or pyrimidine base;

R^1, R^2 and R^3 are independently H, phosphate or a stabilized phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; an amino acid residue; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;

wherein R^2 is not hydrogen;

R^6 is alkyl, CH_3, CF_3, azido, cyano, alkenyl, alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, chloro, bromo, fluoro, iodo, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

X is O, S, SO_2 or CH_2.

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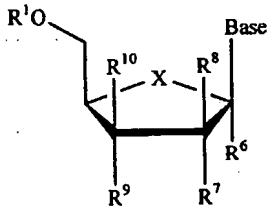
10. A compound of Formula XIII, or a pharmaceutically acceptable salt thereof:



(XIII)

wherein:

Base is a purine or pyrimidine base;

R^1, R^2 and R^3 are independently H, phosphate or a stabilized phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl; arylsulfonyl; aralkylsulfonyl; a lipid; an amino acid; an amino acid residue; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;

R^6 is alkyl, CH_3, CF_3, azido, cyano, alkenyl, alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), CF_3, chloro, bromo, fluoro, iodo, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$;

R^7 and R^9 are independently hydrogen, OR^2, hydroxy, alkyl, azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$;

wherein at least one of R^7 and R^9 is OR^2, wherein each R^2 is independently phosphate or stabilized phosphate; straight chained, branched or cyclic alkyl; acyl; CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, sulfonate ester, wherein the phenyl group is optionally substituted with one or more substituents; alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, a lipid; an amino acid; and amino acid residue, a carbohydrate; a peptide; cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^2 is H or phosphate;

R^8 and R^{10} are independently H, alkyl, chlorine, bromine or iodine;

alternatively, R^7 and R^{10}, R^8 and R^9, or R^8 and R^{10} can come together to form a pi bond; and

X is O, S, SO_2 or CH_2.

11. A method for the treatment of a host infected with a *Flaviviridae* virus, comprising administering an effective treatment amount of a compound or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1-10.

12. The method of claim 11, wherein the virus is hepatitis C.

13. The method of claim 11, wherein the compound or pharmaceutically acceptable salt thereof, is administered in combination or alternation with a second anti-viral agent.

14. The method of claim 13 wherein the second anti-viral agent is selected from the group consisting of an interferon, a ribavirin, an interleukin, a NS3 protease inhibitor, a cysteine protease inhibitor, a phenan-threnequinone, a thiazolidine derivative, a thiazolidine, a benzanilide, a phenan-threnequinone, a helicase inhibitor, a polymerase inhibitor, a nucleotide analogue, a gliotoxin, a cerulenin, an antisense phosphorothioate oligodeoxynucleotide, an inhibitor of IRES-dependent translation, and a ribozyme.

15. The method of claim 14, wherein the second ant-viral agent is an interferon.

16. The method of claim 15, wherein the second agent is selected from the group consisting of pegylated interferon alpha 2a, interferon alphacon-1, natural interferon,

albuferon, interferon beta-1a, omega interferon, interferon alpha, interferon gamma, interferon tau, interferon delta and interferon gamma- 1b.

17. The method of claim 11, wherein the compound or pharmaceutically acceptable salt thereof, is in the form of a dosage unit.

18. The method of claim 17, wherein the dosage unit contains 50 to 1000 mg or 0.1 to 50 mg of the compound.

19. The method of claim 17, wherein the dosage unit is a tablet or capsule.

20. The method of claim 11, wherein the host is a human.

21. The method of claim 11, wherein the wherein the compound or pharmaceutically acceptable salt thereof, is in substantially pure form.

22. The method of claim 11, wherein the compound or stereoisomeric or tautomeric form thereof, or pharmaceutically acceptable salt thereof, is at least 90% by weight of the β-D-isomer.

23. The method of claim 11, wherein the compound or stereoisomeric or tautomeric form thereof, or pharmaceutically acceptable salt thereof, is at least 95% by weight of the β-D-isomer.

24. The method of claim 11, wherein the compound is in the form of a pharmaceutically acceptable salt selected from the group consisting of a tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorate, α-ketoglutarate, α-glycerophosphate, formate, fumarate, propionate, glycolate, lactate, pyruvate, oxalate, maleate, salicylate, sulfate, nitrate, bicarbonate, carbonate salts, hydrobromate, hydrochloride, di-hydrochloride, and phosphoric acid salt.

25. The method of claim 24, wherein the pharmaceutically acceptable salt is a hydrochloride salt.

26. A pharmaceutical composition comprising a compound of any of claims 1 to 10, or a pharmaceutically acceptable salt thereof.

27. The pharmaceutical composition of claim 26, further comprising a pharmaceutically acceptable carrier, diluent or excipient.

28. The pharmaceutical composition of claim 26 comprising an effective amount of the compound or a pharmaceutically acceptable salt thereof, for the treatment of a host infected with a *Flaviviridae* virus.

29. The composition of claim 28, wherein the *Flaviviridae* virus is hepatitis C.

30. The pharmaceutical composition of claim 26, wherein the compound or a pharmaceutically acceptable salt thereof, is in the form of a dosage unit.

31. The composition of claim 30, wherein the dosage unit contains 50 to 1000 mg or 0.1 to 50 mg of the compound.

32. The composition of claim 30, wherein said dosage unit is a tablet or capsule.

33. The pharmaceutical composition of claim 26, further comprising a second anti-viral agent.

34. The pharmaceutical composition of claim 33, wherein the second anti-viral agent is selected from the group consisting of an interferon, a ribavirin, an interleukin, a NS3 protease inhibitor, a cysteine protease inhibitor, a phenan-threnequinone, a thiazolidine derivative, a thiazolidine, a benzanilide, a phenan-threnequinone, a helicase inhibitor, a polymerase inhibitor, a nucleotide analogue, a gliotoxin, a cerulenin, an antisense phosphorothioate oligodeoxynucleotide, an inhibitor of IRES-dependent translation, and a ribozyme.

35. The pharmaceutical composition of claim 34, wherein the second anti-viral agent is an interferon.

36. The pharmaceutical composition of claim 35, wherein the second agent is selected from the group consisting of pegylated interferon alpha 2a, interferon alphacon-1, natural interferon, albuferon, interferon beta-1a, omega interferon, interferon alpha, interferon gamma, interferon tau, interferon delta and interferon gamma- 1b.

37. The pharmaceutical composition of claim 26, or pharmaceutically acceptable salt thereof, is in substantially pure form.

38. The pharmaceutical composition of claim 26, wherein the compound or pharmaceutically acceptable salt thereof; is at least 90% by weight of the β-D-isomer.

39. The pharmaceutical composition of claim 26, wherein the compound or pharmaceutically acceptable salt thereof; is at least 95% by weight of the β-D-isomer.

40. The pharmaceutical composition of claim 26, further comprising a pharmaceutically acceptable carrier suitable for oral, parenteral, inhalant or intravenous delivery.

41. The pharmaceutical composition of claim 26, wherein the compound is in the form of a pharmaceutically acceptable salt selected from the group consisting of a tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorate, α-ketoglutarate, α-glycerophosphate, formate, fumarate, propionate, glycolate, lactate, pyruvate, oxalate, maleate, salicylate, sulfate, nitrate, bicarbonate, carbonate salts, hydrobromate, a hydrochloride, a di-hydrochloride, and phosphoric acid salt.

42. The pharmaceutical composition of claim 41, wherein the pharmaceutically acceptable salt is a hydrochloride salt.

43. A compound or a pharmaceutically acceptable salt thereof, of any of claims 1 to 10, for use in the treatment of a host infected with a *Flaviviridae* virus.

44. The compound of claim 43, wherein the virus is hepatitis C.

45. The compound of claim 43, wherein the host is a human.

46. The use of a compound or a pharmaceutically acceptable salt thereof, of any of claims 1 to 10 in the manufacture of a medicament for the treatment of a host infected with a *Flaviviridae* virus.

47. The use of claim 46, wherein the virus is hepatitis C.

48. The use of claim 46, wherein the host is a human.